patients with RA after the year 2025. In patients diagnosed prior to this time and requiring reconstructive approaches for joint damage, techniques will be developed for resurfacing joints with autologously generated cartilage.

**REFERENCES**


**Research Advances in Systemic Lupus Erythematosus**

Robert P. Kimberly, MD

**Systemic lupus erythematosus** is an autoimmune disease with a significant genetic component to susceptibility. Some environmental risks are known, and identification of specific genetic factors promises to define new molecular targets for therapy. Broad immunosuppression will be replaced by early, selective, and individualized intervention. Mortality rates will decline, and insights into therapy may apply to other autoimmune conditions.

**Major Clinical and Research Advances**

Clinical management of SLE is based on use of nonsteroidal anti-inflammatory drugs (NSAIDs), the addition of hydroxychloroquine and other agents originally developed as antimalarials, targeted and judicious use of glucocorticoids, including large intravenous doses, and aggressive use of other immunosuppressive agents, such as cyclophosphamide. Vigorous management of comorbid conditions, including hypertension and infection, has decreased mortality in persons with SLE.2,3

The immune system plays a crucial role in the pathogenesis of both active inflammatory and noninflammatory mechanisms of organ damage in SLE. Autoreactivity encompasses a broad range of specificities that can include inciting antigens and other antigens through spreading of the immune response. Nucleosomes, apoptotic material, and efficient pathways for routine, nonimmunogenic clearance appear pivotal in pathogenesis of SLE. Equally, effector pathways for inflammation are critical for the development of end-organ damage.

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Lupus involves abnormal activity of the immune system in response to environmental stimuli encountered by the genetically susceptible host. Family studies emphasize the heritability of the SLE diathesis, but susceptibility is polygenic, involving multiple genes with a threshold effect. Deficiencies of complement and other opsonins, genetic variants of IgG and C-reactive protein receptors, and inflammatory cytokine promoter variants have been implicated as components of genetic susceptibility factors.4 Breaks in tolerance and immune hyperactivity lead to tissue injury by both myeloid and lymphoid effector cells. The presence of autoantibodies and autoreactive T cells indicates broad involvement of the immune system, and noninflammatory mechanisms also contribute to vascular and organ injury.

Animal models and clinical observations suggest that different sets of genes can produce similar clinical phenotypes. Consequently, identification of both environmental events and gen-

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Gene therapy for such a complex genetic disease will be used first for drug delivery, not germ line modification. Discoveries in one autoimmune disease will have lessons and applications for other diseases. More targeted therapies will replace broad, nonspecific immunosuppression for most treatment.

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**REFERENCES**


